Retinal processing: **Amacrine cells keep it short and sweet**

Leon Lagnado

A recent study suggests a neuronal circuit in the retina by which amacrine cells contribute to the generation of transient responses in ganglion cells, thereby enabling the visual system to detect changes in light intensity.

Address: MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK.
E-mail: ll1@mrc-lmb.cam.ac.uk

Current Biology 1998, 8:R598–R600
http://biomednet.com/elecref/09609822008R0598

Vision is one of the most intensively studied aspects of brain function. The processing of visual signals begins in the retina, which has several advantages for those interested in investigating how a neural circuit extracts and represents information [1]. The input to the circuit, light, can be easily controlled, and the output can be recorded by monitoring the electrical activity of ganglion cells — the neurons that send fibres along the optic nerve. The processing of visual signals within the retina can be analyzed in detail because the organization of synaptic connections is well understood (Figure 1), and light responses can be recorded from all the major types of neuron. The properties of individual neurons can also be investigated when they have been isolated from the rest of the circuit.

Figure 1

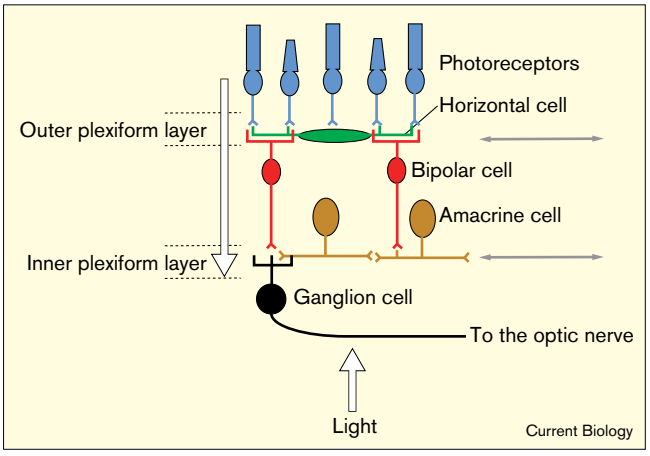


Diagram of the retina showing the principal types of neuron and their synaptic connections. Grey arrows indicate directions of information flow. Signals can pass from photoreceptors to ganglion cells through bipolar cells. Signals can also pass laterally, through horizontal cells at the first synaptic stage in the outer plexiform layer, and through amacrine cells in the second synaptic stage in the inner plexiform layer. Horizontal cells and amacrine cells provide feedback to modulate signals transferred across synapses at these first and second stages.

From the earliest studies of retinal function, it became apparent that many ganglion cells respond strongly just after light is turned on or off, but only weakly if the light is kept on or off (Figure 2). Such ganglion cells are called transient, and their ability to respond to changes in light intensity is a fundamental feature of retinal processing because they extract information about the timing of a stimulus. A recent paper by Roska *et al.* [2] suggests a circuit to explain how neurons within the retina generate transient responses in ganglion cells.

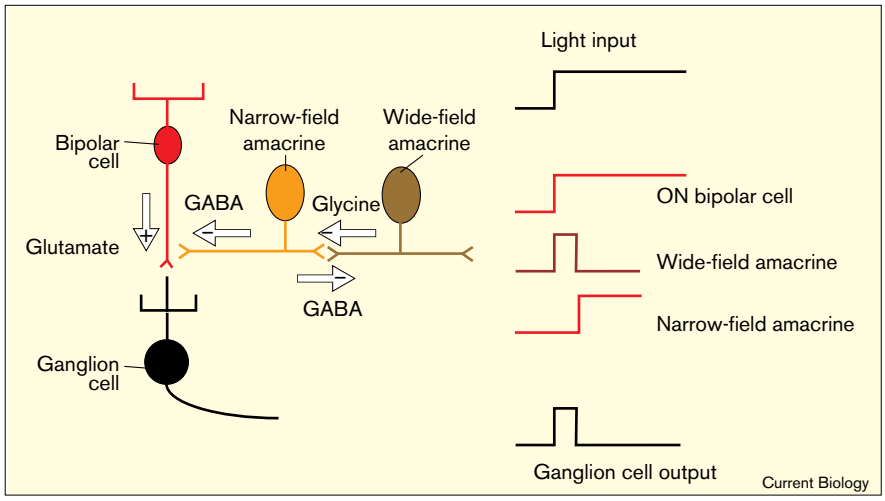
The most direct pathway by which a visual signal is transmitted through the retina is from photoreceptors, which convert light into an electrical signal, to bipolar cells and then to ganglion cells (Figure 1). The neurotransmitter in this pathway is glutamate. Unlike most other neurons in the brain, photoreceptors and bipolar cells do not generate action potentials, but instead generate relatively maintained voltage changes that are graded with the intensity of the light. The generation of transient responses in ganglion cells must therefore occur at the next synaptic stage, between bipolar cells and ganglion cells in the inner plexiform layer. Bipolar cells come in two classes: ON cells, which depolarize and so are excited in response to light; and OFF cells, which hyperpolarize and so are inhibited in response to light. Ganglion cells can generate transient responses when light is switched either on or off, but the mechanisms underlying the transient responses of ON cells when the light is switched on have been investigated in more detail.

In addition to the direct pathway, the transfer of signals from bipolar cells to ganglion cells can occur indirectly, through amacrine cells. These neurons are thought to play a critical role in detecting change, because they respond strongly to light going on or off, as well as to movement of light across the retina. Amacrine cells are the first neurons in the visual system to fire action potentials, and also the first to generate transient responses. They send processes laterally along the inner plexiform layer, at the level of the bipolar-to-ganglion cell synapse (Figure 1). Amacrine cells come in a variety of shapes and sizes, and probably have a number of different functions, although a large number release the inhibitory neurotransmitters γ-amino butyric acid (GABA) and glycine [3].

Many ganglion cells can be inhibited by application of GABA, so one possibility is that the response of a ganglion

Figure 2

A possible circuit for the generation of transient ON responses in ganglion cells, suggested by the work of Roska *et al.* [2]. The left-hand side shows the synaptic connections between neurons in the inner plexiform layer of the retina, and the neurotransmitters used. The right-hand side shows the timing of excitatory signals in these neurons. The output from the ganglion cell indicates when the light was turned on, but not the fact that the light stays on. The excitatory signal transferred from bipolar cells to ganglion cells is truncated by the inhibitory transmitter GABA, released when the narrow-field amacrine responds to light. The delay in this response is caused by inhibition from glycinergic wide-field amacrine cells that respond to light first. GABAergic amacrine cells also truncate the responses of glycinergic amacrines.



cell is shortened — made transient — because of inhibition by GABAergic amacrine cells. The duration of the response in a ganglion cell would be determined by the delay between receiving the excitatory signal from an ON bipolar cell and the inhibitory signal from the amacrine cell. A second possibility is that amacrine cells inhibit ganglion cell responses indirectly, by reducing the signal transferred across the bipolar-to-ganglion cell synapse. This scheme is suggested by two observations: GABAergic amacrine cells make feedback synaptic connections onto bipolar cell terminals, and inhibitory responses can be generated in isolated bipolar cells by the application of GABA to the terminal [4].

The strong circumstantial evidence for involvement of amacrine cells in generating the transient responses of ganglion cells was recently bolstered by a direct experimental test. As described in a recent dispatch [5], Nirenberg and Meister [6] used a cell-ablation technique to remove a population of GABAergic amacrine cells from the mouse retina and found that, as a result, transient ON ganglion cell responses were changed into prolonged discharges.

To investigate the generation of transient ganglion cell responses, Roska *et al.* [2] measured the timing of light responses in bipolar, amacrine and ganglion cells in the salamander retina. The salamander retina is very similar in basic organization and function to the mammalian retina, but it has the advantage of unusually large cells [1]. The salamander retina can be sliced [7], allowing recording electrodes to be placed onto identified neurons in the inner layers. Most ganglion cells in the salamander retina respond transiently, for only about 150 milliseconds after light is turned on. Previous work indicated that this response is shortened by the indirect mechanism — feedback inhibition of neurotransmitter release from the bipolar cell onto the ganglion cell [8]. A crucial aspect of this model is that there must be a delay of about 150 milliseconds between the initial excitation of the ON bipolar cell and the negative feedback signal received from GABAergic amacrine cells. How is this delay set? The new results of Roska *et al.* [2] suggest that it is determined by the interaction between two classes of amacrine cell.

Previous work had shown that many amacrine cells in the salamander retina can be distinguished according to how far they extended processes laterally: 'narrow-field' amacrine cells extend over about 150 μm, while 'wide-field' amacrine cells extend about 400 μm. The two classes make synaptic connections with each other and both contain receptors for glycine and GABA, but they are thought to release different transmitters. The wide-field cells release glycine, while the narrow-field cells release GABA. It is the GABAergic narrow-field cells that synapse onto bipolar cell terminals. Roska *et al.* [2] were able to identify the type of amacrine cell that they had recorded from by measuring the extent of their processes after filling them with a fluorescent dye.

Roska *et al.* [2] found that narrow-field amacrine cells were excited by light with a delay of about 150 milliseconds, but this delay could be shortened by blocking glycine receptors with strychnine. They therefore proposed that GABAergic (narrow-field) amacrines are inhibited by glycinergic (wide-field) amacrine cells, and that this inhibition sets the delay between turning on the light and the release of GABA onto the bipolar cell terminal (Figure 2). Two predictions of this model were borne out. First, wide-field amacrine cells responded to light before narrow-field cells, as would be expected if the response of GABAergic cells was inhibited by glycinergic cells. Second, the ON response of ganglion cells was suppressed by the application of strychnine, as

would be expected of a manoeuvre that caused GABAergic amacrine cells to respond more rapidly, and therefore inhibit ON bipolar cells with a shorter delay.

Although the results of Roska *et al.* [2] indicate that glycinergic amacrine cells inhibit those that are GABAergic, they also found evidence for inhibition the other way round (Figure 2). Blocking the GABAergic input to wide-field amacrine cells with bicuculline caused them to respond to light much more strongly, converting a transient response into a maintained one. If there is reciprocal inhibition between these two classes of amacrine cell, the delayed inhibition of ON ganglion cells must depend critically on the fact that glycinergic cells respond to light before GABAergic cells. This might occur because glycinergic (wide-field) amacrine cells receive stronger input from a larger number of ON bipolar cells and/or because they have a lower voltage threshold for the generation of action potentials.

The work of Roska *et al.* [2] is a significant step forward because it suggests an explanation for the delay in the feedback circuit that converts a maintained light input into a transient ganglion cell response. The idea that negative feedback is provided by GABAergic amacrine cells [4,6,8] can now be coupled to the idea that the delay in this feedback is caused by glycinergic amacrine cells. The evidence relies on the use of pharmacological blockers of synaptic transmission perfused over the whole retina, so one cannot rule out the possibility that GABAergic and glycinergic synapses at sites other than those shown in Figure 2 also play a role in generating transient responses. It should, however, be possible to test this model further. Perhaps the technique used by Nirenberg and Meister [6] to ablate GABAergic amacrine cells can be used to ablate glycinergic amacrine cells, when one would predict that the delay in the negative feedback would be shortened, making ganglion cell responses to light onset even more transient. The combination of anatomical, physiological and molecular biological techniques with which it is possible to investigate retinal function will provide an increasingly detailed understanding of how neural circuits detect change.

References

1. Dowling JE: *The Retina: An Approachable Part of the Brain*. Cambridge, Massachusetts: Harvard University Press; 1987.
2. Roska B, Nemeth E, Werblin FS: **Response to change is facilitated by a three-neuron disinhibitory pathway in the tiger salamander Retina.** *J Neurosci* 1998, **18:**3451-3459.
3. Wässle H, Boycott BB: **Functional architecture of the mammalian retina.** *Physiol Rev* 1991, **71:**447-480.
4. Tachibana M, Kaneko A: **Gamma-aminobutyric acid exerts a local inhibitory action on the axon terminal of bipolar cells: evidence for negative feedback from amacrine cells.** *Proc Natl Acad Sci USA* 1987, **84:**3501-3505.
5. Mobbs P, Attwell D: **Retinal processing: Visionary transgenics.** *Curr Biol* 1997, **7:**R483-R486.
6. Nirenberg S, Meister M: **The light response of retinal ganglion cells is truncated by a displaced amacrine circuit.** *Neuron* 1997, **18:**637-650.
7. Werblin FS: **Transmission along and between rods in the tiger salamander retina.** *J Physiol* 1978, **280:**449-470.
8. Lukasiewicz PD, Werblin FS: **A novel GABA receptor modulates synaptic transmission from bipolar to ganglion and amacrine cells in the tiger salamander retina.** *J Neurosci* 1994, **14:**1213-1223.